PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference C1-A0603Y1P	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/JP2007/057058	International filing date *(day/month/year)* 30 March 2007 (30.03.2007)	Priority date *(day/month/year)* 31 March 2006 (31.03.2006)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant CHUGAI SEIYAKU KABUSHIKI KAISHA		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 21 October 2008 (21.10.2008)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Masashi Honda e-mail: pt08.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)*
Applicant's or agent's file reference C1-A0603Y1P	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2007/057058	30.03.2007	31.03.2006

International Patent Classification (IPC) or both national classification and IPC

Applicant
CHUGAI SEIYAKU KABUSHIKI KAISHA

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/JP	Date of completion of this opinion	Authorized officer
Facsimile No.		Telephone No.

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Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ the translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rule 12.3(a) and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☒ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☒ in electronic form

c. time of filing/furnishing

☒ contained in the international application as filed

☐ filed together with the international application in electronic form

☐ furnished subsequently to this Authority for the purposes of search

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	7, 16, 30, 31, 34-37	YES
	Claims	1-6, 8-15, 17-29, 32, 33	NO
Inventive step (IS)	Claims	34-37	YES
	Claims	1-33	NO
Industrial applicability (IA)	Claims	1-37	YES
	Claims		NO

2. Citations and explanations:

Document 1: MERCHANT, A. M., et al., An efficient route to human bispecific IgG, Nat. Biotechnol., Vol. 16, No. 7, 1998, p. 677-81 (particularly refer to table 1)

Document 2: MANZKE, O. et al., Single-step purification of bispecific monoclonal antibodies for immunotherapeutic use by hydrophobic interaction chromatography, J. Immunol. Methods, Vol. 208, No. 1, 1997, p. 65-73 (particularly refer to "Materials and Methods", Section 2.1 and fig. 1, 2B and 3)

Document 3: MARVIN, J. S., et al., Recombinant approaches to IgG-like bispecific antibodies, Acta Pharmacol. Sin., Vol. 26, No. 6, 2005, p. 649-58

Claims 1-6, 8-15, 17-19, 23-27, 29, 32 and 33

The inventions of claims 1-6, 8-15, 17-19, 23-27, 29, 32 and 33 lack novelty and do not involve an inventive step in view of document 1 cited in the ISR.

Document 1 discloses that a bispecific antibody shown in v13 to v16 was obtained by inserting multiple amino acid variants such as E356C in the CH3 region (heavy chain constant region) of CD-4-IgG shown in IA (the first polypeptide) and

anti-CD3H chain shown in Ab (the second polypeptide), introducing it together with an anti-CD3L chain (the third polypeptide including a light chain variable region) into cell 293 to affinity-purify the product from said cell. The first and second polypeptide constituting v13 to v16 described in document 1 include amino acid residues with an electric charge that are substituted by amino acid residues without an electric charge as shown in the variants of E356C, etc., and include multiple variants of amino acid residues with mutually different characteristics, and therefore, it is considered to be possible that the peaks are separated in chromatography with differences in the isoelectric point being the cause.

Claims 20-22

The invention of claims 20-22 lacks novelty and does not involve an inventive step in view of document 1.

Document 1 discloses a bispecific antibody shown in v1 which was produced by inserting the variation shown in K392C (a variant of the lysine in position 392 to cysteine; a variant of amino acid residue with an electric charge to amino acid residue without electric charge) in the CH3 region (heavy chain constant region) of the CD-4-IgG (the first polypeptide) shown in IA and co-expressing it with the anti-CD3H chain (the second polypeptide) shown in Ab.

Claims 30 and 31

The invention described in claims 30 and 31 does not involve an inventive step in view of document 1.

Since producing a pharmaceutical composition including specific antibodies and obtaining nucleic acid are obvious issues in said technical field, making the bispecific antibody described in document 1 a pharmaceutical composition and

obtaining the nucleic acid constituting said antibody is easy for an expert in said technical field.

Claims 9, 19, 23-29, 32 and 33

The inventions described in claims 9, 19, 23-29, 32 and 33 lack novelty and do not involve an inventive step in view of document 2 cited in the ISR.

Document 2 discloses that an IgG2a/IgG1 antibody simultaneously including IgG2a and IgG1 included in Peak1 and Peak3 and having different isoelectric points (a bispecific antibody wherein the heavy chain constant regions with different isoelectric points are IgG1 and IgG2) was produced from hybrid hybridoma, and that Peak2 including said antibody can become a peak separated on the basis of hydrophobic chromatography. The hybrid hybridoma described in document 2 corresponds to a host cell including the nucleic acid which codes the bispecific antibody.

Claims 1-19 and 23-33

The inventions of claims 1-19 and 23-33 do not involve an inventive step in view of documents 1-3 cited in the ISR.

Document 2 discloses that the antibody (Peak1) including IgG2a and the antibody (Peak3) including IgG1 have different isoelectric points, and that the antibody (bispecific antibody) consisting of the heterodimer shown in IgG2a/IgG1 can, to a certain degree, be separated from the IgG2a homodimer and the IgG1 homodimer by performing hydrophobic chromatography.

This means that since document 2 is considered to disclose that, in the production of bispecific antibodies, it is possible to separate bispecific antibodies using

chromatography on the basis of the difference in the isoelectric points if the heavy chain constant region of the two polypeptides constituting the antibody is made IgG2 and IgG1 respectively, and since producing a bispecific antibody using a genetic engineering technique (a technique that expresses the antibody using, for example, the nucleic acid coding the antibody) is also a well-known art in said technical field (for example, refer to documents 1 and 3), it is easy for an expert in said technical field to introduce the nucleic acid coding IgG1 and IgG2 respectively into the nucleic acids coding the first polypeptide and the second polypeptide to achieve a difference in the isoelectric points of the first polypeptide and the second polypeptide constituting the antibody in order to produce a bispecific antibody.

Further, since making it a pharmaceutical composition including specific antibodies and obtaining nucleic acid are obvious issues in said technical field, making the bispecific antibody a pharmaceutical composition and obtaining the nucleic acid constituting said antibody is easy for an expert in said technical field.

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 1-6, 8-15, 17-27 and 29-33

The multi-specific antibody or the method for producing said antibody as described in claims 1-6, 8-15, 17-27 and 29-33 modifies both or any one of the nucleic acids which code the first polypeptide and the second polypeptide to achieve a difference in the isoelectric point and also produces an antibody retaining the multi-specific activity of the antibody, but as a method to modify polypeptides so that they will have different isoelectric points and to produce an antibody retaining the antibody activity, the example, etc., only discloses making the heavy chain constant region in the first polypeptide and the second polypeptide IgG1 and IgG2 or IgG1 and IgG4, which have different isoelectric points, or modifying a specific amino acid residue of the variable region when producing a humanized bispecific PF antibody having the two activities of a humanized A69 antibody and a humanized B26 antibody (the amino acid residue modification shown in SEQ. ID NO: 8, 12, 15, 17 or 18 disclosed in examples 6 and 8), and it is thus unclear - even when considering common general technical knowledge in said field - what kind of technique should concretely be used other than those disclosed in the examples, etc., to be able to modify both or any one of the nucleic acids and also produce an antibody that retains the multi-specific activity of the antibody (particularly regarding the method to modify the amino acid residue in the variable region portion of the antibody, it is highly probable that the binding activity of the antibody changes when introducing a variant to the variable region, and one must, for each antibody, decide the position and type of the amino acid that the variant should be inserted into, and therefore,

Box No. VIII Certain observations on the international application

it is unclear what method other than that disclosed in the Examples should be used.)

Consequently, claims 1-6, 8-15, 17-27 and 29-33 cannot be considered to be supported by the description, and also do not contain clear and sufficient disclosures allowing an expert in said technical field to implement them.

Claims 34-37

Regarding the multi-specific antibody described in claims 34-37, the examples of the description, etc., only disclose that, when a bispecific antibody was expressed using three polypeptides shown in SEQ ID NO: 8, 15 and 17, or SEQ ID NO: 12, 15 and 18, respectively, it retained the antibody activity, and even when considering common general technical knowledge in said field, it is unclear whether multi-specific antibodies that retain antibody activity can be obtained using polypeptides other than those disclosed in the examples, etc. (SEQ ID NO: 8, 12, 15, 17 or 18).

Consequently, claims 34-37 cannot be considered to be supported by the description, and also do not contain clear and sufficient disclosures allowing an expert in said technical field to implement them.

Claims 1-7, 9-16, 18-28 and 30-37

The inventions of claims 1-7, 9-16, 18-28 and 30-37 relate to a "multi-specific antibody", but the description only discloses that a bispecific antibody was produced using a first polynucleotide and a second polynucleotide, and even when considering common general technical knowledge in said field, it is unclear concretely what kind of "multi-specific antibody" other than a bispecific antibody constituted from polypeptides can be produced.

Box No. VIII Certain observations on the international application

Consequently, claims 1-7, 9-16, 18-28 and 30-37 cannot be considered to be supported by the description, and also do not contain clear and sufficient disclosures allowing an expert in said technical field to implement them.

Claims 2, 10, 11 and 23

Even when considering the disclosures of the description and common general technical knowledge in this field, it is unclear concretely what kind of chromatography the text "standard chromatography" in claims 2, 10, 11 and 23 indicates.

Therefore, claims 2, 10, 11 and 23 are not described clearly and briefly.

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: International Patent Classification (IPC)

C12N15/09(2006.01)i, A61K39/395(2006.01)i,
A61P43/00(2006.01)i, C07K16/00(2006.01)i,
C07K19/00(2006.01)i, C12N1/15(2006.01)i,
C12N1/19(2006.01)i, C12N1/21(2006.01)i,
C12N5/10(2006.01)i, C12P21/02(2006.01)i